ATTACHMENT A
Remarks

Claims 1-9 are pending in the present application. By this Amendment, Applicants have amended claims 1, 4, 5 and 7. Applicants respectfully submit that the present application is in condition for allowance based on the discussion which follows.

The abstract of disclosure was objected to for not being included on a separate sheet of paper, citing M.P.E.P. § 608.01(b). However, contrary to this rejection, the cited M.P.E.P. section is not relevant to the present application, which is a National Stage 371 application, and, as such, the published PCT application includes an abstract on a separate page. Therefore, the rejection is "improper" (see M.P.E.P. § 1893.03(e)).

The specification was objected to for the use of the trademark "NAFION" which was not indicated as being a trademark. By this Amendment, Applicants have amended the specification to note NAFION as a trademark by using all caps, in accordance with conventional U.S. patent practice.

Claims 1-9 were rejected under 35 U.S.C. § 112, second paragraph. Specifically with regard to claim 1, claim 1 was rejected for the use of the trademark, NAFION. By this Amendment, Applicants have amended claim 1 to remove reference to the trademark, now only referring to the generic name. In addition, claim 1 was rejected for being indefinite with regard to the phrase, "the electrochemical outcome," which, by this Amendment, Applicants have amended to now recite, "an electrochemical outcome." Finally, claim 1 was rejected for using the phrase, "thereby providing an output signal related to the composition of the fluid." By this Amendment, Applicants have amended the last line of claim 1 to now recite, "thereby providing an output signal relating to the concentration of one or more analytes comprising glucose in the fluid" to thereby more

clearly recite how determining the analytes comprising glucose in the body fluid relates to the preamble of claim 1.

In addition, claim 4 was rejected as being indefinite for not clearly indicating whether the one or more analytes includes glucose, as recited in claim 1. By this Amendment, Applicants have amended claim 4 to more clearly recite that the one or more analytes comprises glucose.

Finally, claim 7 was rejected under 35 U.S.C. § 112, second paragraph for lacking antecedent basis for the phrase "prior to determination." By this Amendment, Applicants have amended claim 7 to more clearly recite that prior to applying a varying potential to the working electrode, the sample of the fluid is made more alkaline or acidic, thereby complying with the requirements of 35 U.S.C. § 112, second paragraph.

Claims 1-9 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Say et al. (U.S. Patent No. 6,134,461) (hereinafter "Say") in view of Saini et al. (WO 00/20855) (hereinafter "Saini").

Say discloses an electrochemical method and apparatus for determining analytes, with glucose mentioned as a possible analyte. After the description of specific embodiments, there is a discussion of "a variety of optional items [which] may be included in the sensor" (Say, column 23, line 51). One of these is an "interferent-eliminating layer." See, e.g., Say, column 25, line 38 to column 26, line 8. At column 25, lines 51 to 55, it is stated that: "The interferent-eliminating layer may include ionic components, such as NAFION, incorporated into a polymeric matrix to reduce the permeability of the interferent-eliminating layer to ionic interferents having the same charge as the ionic components."

The present application teaches, for the first time, an entirely different effect of NAFION, perfluorosulfonic acid polymer, than disclosed in the prior art. The data presented in the present application show that NAFION specifically enhances the detection of glucose (and may also enhance the detection of other metabolites). Accordingly, the present method, based on the new discovery, is novel over the prior art.

The present specification, starting on page 16 in line 8, refers to detection of glucose, and the effect of the presence of a NAFION membrane. Figure 5 shows some results. It shows that when an electrode is modified with NAFION, the electrochemical reaction of glucose is fast. This is shown by the well-resolved redox peaks at about -0.2V. The line for "0mM, 5% NAFION" shows a small peak at about -0.2V. This is due to the residual levels of glucose in blood. It should be noted that a clerical error, obvious to one skilled in the art, is present in Figure 5, where the legend "25 mM, 0% NAFION" (emphasis added) is incorrect with regard to the NAFION amount, as the plot line and disclosure describing Figure 5 (specification, page 16, lines 16-18) is consistent with the presence of NAFION. In fact, the correct legend, consistent with the data shown in Figure 5, should have read "25 mM, 5% NAFION."

In comparison, for experiments without NAFION, the redox peak due to glucose oxidation is broad (see the line labeled "15mM, 0% NAFION"). Furthermore, no signal is visible for residual glucose levels in the absence of NAFION (line labeled "0mM, 0% NAFION"). In other words, unmodified electrodes are not sensitive enough to pick up the residual glucose because of the slower electron transfer kinetics.

In electrochemistry, it is well known that narrowly defined redox peaks are indicative of fast electron transfer between the compound of interest and the electrode. In contrast, a broadly defined redox peak indicates slower electron transfer. Thus, these data show that NAFION has an enhancing effect on the rate of electron transfer between glucose and the electrode. This enhancing effect could not arise from NAFION's known ability to exclude macromolecules, as the latter property would not affect the redox chemistry of glucose, as shown by the shape of the redox peaks in Figure 5. The improved peak resolution obtained with NAFION modified electrodes provides greater potential for multi-analyte detection, as each analyte may be more easily distinguished. This is an important property of NAFION for these applications.

Without being restricted to a single explanation for these results, the basis of the enhancement is probably due to a favorable interaction of intermediate products of glucose oxidation with the NAFION film. Glucose oxidation proceeds in a complex multi-step process that involves charged intermediates. Glucose oxidation at neutral pH tends to result in the passivation of the electrode surface due to the build-up of breakdown products. This is because, at neutral pH, the oxidation reaction of glucose is relatively slow, which allows time for the formation of reactive intermediates that passivate the electrode. However, the effect can be mitigated if the reaction is carried out at extremes of pH (for example, in Figure 4, the glucose oxidation shows well resolved redox peaks in 0.1M NaOH, at pH 12).

The slower reaction at neutral pH is, therefore, likely to occur in body fluids, such as interstitial fluid, which has a normal pH in the range of 7.2-7.4. Figure 5 exemplifies the problem in interstitial fluid, where the redox peaks due to glucose oxidation are

broad (when NAFION is omitted). In contrast, when NAFION is present, the glucose redox peaks become well resolved, suggesting fast electron transfer of glucose in the absence of electrode passivation. In this case, the formation of passivating reactive intermediates does not occur.

The rate enhancement observed with glucose oxidation is likely to arise from ionic interaction between charged glucose intermediates and charged SO_3 groups bonded to the NAFION polymer which appear to favor the oxidation reaction. The acidity of NAFION, owing to an abundance of H^+ ions dissociated from the SO_3 groups, may also promote the glucose oxidation reaction. Thus, NAFION acts specifically to facilitate the detection of metabolites, as referred to on page 13 in line 9 in the present description, and now appreciated in the data of Figure 5.

Based on the foregoing, the use of NAFION membranes brings an unexpected and significant advantage to glucose detection, over what is taught in the prior art. For example, no such effect is taught by Say. Say does not have an actual example using NAFION. The only disclosure of NAFION is as one possible component in one optional layer.

In summary, the present inventors have now discovered that NAFION provides a particular advantageous effect in the detection of glucose, which is surprising and unexpected in view of Say, individually or in combination with Saini. Since the effect was not known from Say, one of ordinary skill in the art would not have been led to develop the present method of determining one or more analytes comprising glucose, as claimed.

Based on the foregoing, Applicants respectfully submit that claims 1-9 are not obvious from Say in view of Saini.

In view of the foregoing, Applicants respectfully submit that the present application is in condition for allowance.

END REMARKS